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REVIEW

Association of response endpoints with survival outcomes in multiple myeloma

S Lonial¹ and KC Anderson²

Since the introduction of the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, more patients with multiple myeloma are achieving deep, durable responses and disease control, and are living longer. These improvements have afforded more robust analyses of the relationship between response and survival. Generally, these studies have demonstrated that improvements in the quality of response across all stages of treatment are associated with better disease control and longer survival. Thus, achievement of maximal response should be strongly considered, particularly in the frontline setting, but must also be balanced with tolerability, quality of life and patient preferences. In select patients, achievement of a lesser response may be adequate to prolong survival, and attempts to treat these patients to a deeper response may place them at unnecessary risk without significant benefit. Maintenance therapy has been shown to improve the quality of response and disease control and, in some studies, survival. Studies support maintenance therapy for high-risk patients as a standard of care, and there are emerging data supporting maintenance therapy in standard-risk patients to improve progression-free and possibly overall survival. Multidrug regimens combining a proteasome inhibitor and an IMiD have shown exceptional response outcomes with acceptable increases in toxicity in both the frontline and salvage settings, and are becoming a standard treatment approach. Moving forward, the use of immunophenotypic and molecular response criteria will be essential in better understanding the impact of highly active and continuous treatment regimens across myeloma patient populations. Future translational studies will help to develop antimyeloma agents to their fullest potential. The introduction of novel targeted therapies, including the IMiD pomalidomide and the proteasome inhibitors carfilzomib and ixazomib (MLN9708), will provide greater options to individualize treatment and help patients achieve a clinically meaningful response.

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INTRODUCTION

Over the past decade, the introduction of targeted therapy with the proteasome inhibitor (PI) bortezomib (approved by the US Food and Drug Association in 2003) and immunomodulatory drugs (IMiDs) lenalidomide and thalidomide (both approved in 2006) have vastly improved the outcomes for patients with multiple myeloma (MM).^{1–3} When used alone or as part of combination regimens, these therapies have been shown to provide deep and durable, quality responses, which have translated into advances in disease control and survival. During the early years of their use from 2003 to 2006, the 5-year survival estimate in MM increased to 40.3% compared with 32.8% between 1998 and 2002.² Unfortunately, most patients still face the challenges of disease progression and eventually succumb to the disease.

The treatment paradigm for MM is evolving, but the general goals continue to include rapid disease control to reverse complications, extending disease control and survival, and maintaining quality of life.^{4–6} In recent years, a growing body of evidence indicates a relationship between the quality of response to treatment (depth and durability) and clinical outcomes. Before the introduction of targeted therapies, most patients were unable to achieve quality responses without undergoing high-dose therapy with autologous stem cell transplant (HD-ASCT). Given

that HD-ASCT was initially limited to patients under 65 years of age and MM has a median onset of 70 years,⁵ many patients were ineligible for transplantation and instead received a less-intensive treatment. As a consequence, achievement of a deep and durable response was rare and thus, it was challenging to relate response and survival.^{7–10} Furthermore, these studies generally excluded high-risk patients for whom the benefit of achieving and maintaining a complete response (CR) is more evident.¹¹

The rapid adoption of targeted therapies has afforded a greater focus on depth and duration of response and their impact on outcomes.^{12–17} Both transplant-eligible and -ineligible patients now achieve quality responses, including CRs, across all phases of treatment (induction, consolidation, maintenance and salvage).¹⁸ The development of triplet combinations that combine a PI with an IMiD and a corticosteroid or chemotherapy has provided unprecedented levels of response in the frontline and relapsed settings in high-risk patients.^{19–25} Generally, studies with targeted therapies support an aggressive treatment paradigm to maximize the quality of response and minimize the burden of the malignant clone, particularly in the early treatment phase.^{26–32} Even at the time of presentation multiple clones can be present. Theoretically, an aggressive upfront treatment strategy may improve the depth and durability of response and inhibit clonal evolution, but clinical studies are needed to support this premise.^{33–35}

¹Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA and ²Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA. Correspondence: Dr S Lonial, Hematology and Medical Oncology, Emory University, 1365 Clifton Rd, Building C, room 4004, Atlanta, GA 30322, USA. E-mail: sloni01@emory.edu

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However, there are important considerations.^{6,36,37} Quality of response alone is not a validated surrogate marker of overall survival (OS).³⁸ There are currently no definitive data to validate the association between quality of response and survival outcomes. Moreover, the association of depth of response with outcomes is not universal across studies. Biologically, MM is a spectrum of diseases and its course and response to therapy can be highly variable. Some patients achieve very good initial responses that are short-lived, whereas others achieve only minimal responses (MRs) that are durable and clinically relevant.^{39–41} Furthermore, aggressive treatment can be associated with greater toxicity than conventional approaches, and thus, the risk-to-benefit must be compared with alternative approaches that favor 'disease control' with less-intensive sequential regimens.^{6,37} Both strategies have merit but in the context of specific patient populations and disease characteristics. Risk-adapted strategies favor aggressive treatment in high-risk patients and more conventional approaches in standard-risk patients.⁵ However, risk stratification is not sufficiently accurate to predict the quality of a treatment response for individual patients. Undertreatment could result in failure to achieve a potential cure in standard-risk patients or rapid loss of disease control in high-risk patients. For these reasons, it may be preferable to maximize the response of all patients at diagnosis and use personalized treatment in the consolidation and maintenance phases.

In view of the evolving treatment strategies in MM, it is important to consider the impact depth of response has on clinical outcomes collectively and within the various treatment phases and disease settings. Although current data do not address all gaps in our knowledge, they do help to better inform treatment decisions. Here, we provide an overview of studies that have explored the impact of quality of response on outcomes by transplant status and stage of treatment, and consider our knowledge gaps. We review recent studies of triplet combinations and highlight the need for more sensitive response criteria that will better inform short- and long-term treatment decisions.

DEPTH OF RESPONSE AND CLINICAL OUTCOMES

A number of caveats to the data reviewed here should be acknowledged upfront. It is important to keep in mind that before 1998 multiple response criteria were in use with variable definitions for CR or no definition at all.^{9,10,42,43} In 1998, the European Group for Bone Marrow and Blood Transplantation developed the first uniform response criteria for MM based on: monoclonal paraprotein serum and urine levels with electrophoresis and immunofixation; the proportion of plasma cells in the bone marrow aspirates/biopsies with histologic and cytologic studies; bone lesions and soft tissue plasmacytomas, with radiographic imaging and clinical evaluations.⁴⁴ Response categories included CR, partial response (PR), MR, stable disease and progressive disease. Then, in 2006, the International Myeloma Working Group developed response criteria similar to that of European Group for Bone Marrow and Blood Transplantation but with some differences, including the addition of stringent CR and very good partial response (VGPR) response categories.⁴⁵ Studies also sometimes use near CR (nCR) as an additional response category.⁴⁶

We also acknowledge that many of the studies discussed here are retrospective, observational or exploratory analyses with limited number of patients. Patient populations and treatments were more homogeneous and well controlled in some studies than in others. Also, survival data may be confounded by the impact of subsequent or salvage therapies at the time of progression,^{1,3,47–49} which may vary based on the depth and duration of the initial response and access to treatments. Analysis of outcomes by the level of response may introduce selection bias, with standard-risk patients being more likely to achieve a quality

response than high-risk patients. It is not surprising that studies have reported no association between depth of response and outcomes, but generally these studies were conducted before the advent of the targeted therapy era.^{9,42,50–53}

In the targeted therapy era, more patients across the myeloma spectrum are achieving quality responses with improved survival outcomes. In a meta-analysis of phase 3 bortezomib trials that included 2086 transplant-eligible patients,⁵⁴ the use of bortezomib during induction significantly improved overall response rate (ORR), \geq VGPR and CR compared with non-bortezomib regimens, which corresponded to improvements in progression-free survival (PFS) and OS. Despite the lack of definitive data, the body of evidence linking quality of response to outcomes is growing and has become more compelling.

Newly diagnosed MM

Several studies have assessed the impact of response levels on outcomes in patients with newly diagnosed MM (NDMM) receiving HD-ASCT (Table 1). In general, studies show that a quality response at each treatment stage—induction, HD-ASCT, and consolidation—is associated with improved outcomes.^{19,26,55,56} Lahuerta *et al.*²⁶ evaluated response in 632 patients with NDMM treated with the GEM2000 protocol, which used a chemotherapy induction regimen followed by HD-ASCT. Post transplantation, there was a significant association between response level and outcomes with a 5-year OS rate of 74% in patients achieving a CR compared with 63% for nCR ($P=0.01$), 50% for PR ($P<0.0001$) and 57% for stable disease ($P=0.01$). Post induction, there were trends of improved survival by level of response, but the association was less robust. There was no difference in OS for achievement of CR post induction versus post transplantation. Outcomes were worse for patients with persistent nCR (before and after transplantation) compared with patients whose response improved to nCR post transplantation with a 5-year OS rate of 45% versus 72% ($P=0.001$). In a separate phase 3 IFM 2005-01 study, which randomized 482 patients to induction with bortezomib and dexamethasone or vincristine, doxorubicin and dexamethasone (VAD), PFS was significantly longer for patients achieving a VGPR post induction compared with post transplantation (median 41.2 versus 31.1 months; $P=0.01$).²⁷ In multivariate analysis, a response \leq VGPR overall and post induction were both retained as negative prognostic factors. Taken together, data from these and other studies^{26,27,55,56} suggest that it is important to attain a quality response early with induction therapy and drive the response further in the subsequent treatment stages.

Studies have also demonstrated the prognostic implications of response durability.^{51,57} Barlogie *et al.*⁵⁷ conducted a retrospective analysis of OS by response at a 36-month landmark in patients enrolled in a total therapy (TT)2 study (double HD-ASCT supported by induction, consolidation and maintenance with thalidomide; $n=668$). Response categories included CR sustained for ≥ 36 months ($n=256$), CR lost before 36 months ($n=39$) and non-CR ($n=211$). Median OS was significantly longer in the sustained CR group (not reached) versus the non-CR group (5.6 years, $P<0.0001$) and the lost-CR group (1.6 years, $P<0.0001$), as well as for the comparison of non-CR to lost-CR ($P<0.0001$). These survival trends were also observed in patients enrolled in a TT1 study as well as a cohort receiving other transplant protocols. Similarly, a pooled analysis of GEM2000 and GEM2005 studies showed that median survival was significantly shorter for patients with unsustained CR at 100 days ($n=29$) compared with those with a lesser response sustained for at least 100 days ($n=667$), and those with a sustained CR ($n=241$)—39 months, 76 months and not reached, respectively ($P<0.001$).⁴¹

As mentioned earlier, a number of caveats of these studies should be considered. Survival outcomes can be confounded by

Table 1. Prognostic impact of response level in patients with newly diagnosed multiple myeloma: transplant studies

Reference Response criteria Study type	Treatment	Response	n	mEFS	5 yr PFS/TTP/EFS (median, mo ^a /rate, %)	P-value 0.05 CR versus PR	mOS	5 yr OS (median, mo ^a /rate, %)	P-value 0.02 CR versus SD
Lahuerta <i>et al.</i> ²⁶ mEBMT Prospective	GEM2000 → HD-SCT → IFN + prednisone (maint)	Post induction	101	56 47 43	53 49 34		NR NR NR	78 65 63	
			346	41 33	32 25		NR NR	56 25	
		Post transplant	26	61	52	<0.01 CR versus nCR, PR and SD	NR	74	≤0.01 CR versus nCR, PR, and SD; 0.04 nCR versus PR
			124	40	27		NR	63	
			175	34	23		61	50	
			30	44	27		NR	57	
			25	13	4		15	24	
Dytfeld <i>et al.</i> ¹¹⁴ mEBMT Phase 2	VDD ± SCT	Post induction	25	PFS	4 yr 67.2	P-value 0.08	OS	4 yr 86.5	P-value 0.04
	VDD + SCT (subgroup)	Post induction	15	—	46.3		—	58.2	
			16	—	77.8	0.036	—	92.9	0.027
			14	mPFS	53.8	P-value <0.001	mOS	64.3	P-value <0.001
Gertz <i>et al.</i> ¹¹⁵ Retrospective	T or R regimen → SCT	Post induction	232	22.1			73.5	—	
			54	13.1			30.4	—	
Moreau <i>et al.</i> ²⁷ mEBMT Ph 3 post hoc	VD or VAD ± DCEP → SCT	Post induction	125	41.2		<0.0001	—	—	—
			357	29.0			OS	5 yr 74	P-value 0.0017
Harousseau <i>et al.</i> ²⁸ EBMT Pooled analysis (2 prospective studies)	VAD → double SCT → no treatment, Pam or Pam + T	Post transplant	445	mEFS	5 yr 34	P-value 0.005	—	61	
			288	32	26		—	—	
Kapoor <i>et al.</i> ¹¹⁶ IMWG Retrospective	SCT	Post transplant	115	—	—		mOS ^b	4 yr ^f 86	P-value 0.007
			28	—	—		NR	60	
			46	—	—		53	—	
Barlogie <i>et al.</i> ⁵⁷ EBMT Retrospective	TT2	36-mo landmark	256	—	—		mOS	4 yr 83	P-value <0.0001 Sust-CR versus non-CR and <0.0001 versus lost-CR; <0.0001 non-CR versus lost-CR 0.06 Sust-CR versus non-CR and 0.001 versus lost-CR; 0.04 <0.0001 Sust-CR versus non- CR/lost-CR; 0.0002 non- CR versus lost-CR
	TT1	36-mo landmark	211	—	—		NR	83	
			39	—	—		67.2	59	
			44	—	—		19.2	19	
			88	—	—		127.2	—	
			33	—	—		34.8	—	
			197	—	—		76.8	—	
			252	—	—		46.8	—	
			60	—	—		21.6	—	
Alegre <i>et al.</i> ¹¹⁷ Observational	HD-ASCT ± IFN-α maint	Post induction	56	mPFS	—	P-value 0.001 CR/PR versus SD/PR	mOS	—	P-value 0.001 CR/PR versus SD/PR
			153	35	—		39	—	
			25	28	—		36	—	
			25	20	—		24	—	
			25	8	—		12	—	
			17	EFS	5 yr 65	P-value 0.025 CR versus <CR 0.006 ≥VGPR versus PR/SD	OS	5 yr 63	P-value 0.31 CR versus <CR
			29	—	—		54	63	
			81	—	—		47	47	
			18	—	—		27	56	
			43	—	—		30	50	
			53	—	—		30	58	
			51	—	—		33	59	
			28	—	—		34	63	

Abbreviations: DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin; GEM2000, induction therapy with six alternating 5-week cycles of vincristine, carmustine, cyclophosphamide, melphalan and prednisone/vincristine, carmustine, doxorubicin and dexamethasone → HD-SCT; HD-ASCT, high-dose therapy with autologous stem cell transplant; IFN, interferon; IMWG, International Myeloma Working Group; maint, maintenance therapy; mEBMT, modified European Group for Blood and Marrow Transplantation; mEFS, median event-free survival; mOS, median overall survival; mPFS, median progression-free survival; nCR, near complete response; NR, not reached; Pam, pamidronate; PD, progressive disease; R, lenalidomide; sCR, stringent complete response; SCT, stem cell transplant; SD, stable disease; Sust, sustained; T, thalidomide; TT; total therapy; VAD, vincristine, doxorubicin, dexamethasone; VD, bortezomib, dexamethasone; VDD, bortezomib, pegylated liposomal doxorubicin, dexamethasone; VGPR, very good partial response; yr, years. ^aConversion to months for studies reporting other time increments. ^bFrom diagnosis. ^cFrom diagnosis. ^dFrom diagnosis. ^eFrom diagnosis. ^fFrom SCT.

the use of subsequent treatments, including maintenance and salvage therapies with targeted therapies. In the IFM 2005-01 study, patients who achieved at least a PR could enroll onto the IFM 2005-02 study of maintenance therapy with lenalidomide.²⁷ Also, the relationship between quality of response and outcomes may be confounded by tumor biology.⁵³ In the pooled analysis of GEM2000 and GEM2005 studies, high-risk cytogenetics was an independent predictor of unsustained CR.⁴¹ On the other hand, subgroup analyses of the IFM 2005-01 study demonstrated that a quality response improved outcomes in high-risk patients. The median PFS was significantly longer in patients with International Staging System (ISS) 2/3 disease who achieved a post-induction VGPR versus those who did not (not reached versus 23 months; $P < 0.0001$), as well as in patients with high-risk cytogenetics (37 versus 24 months, respectively, $P = 0.0036$).

Without a trial specifically designed to assess the quality of response, tumor biology remains a confounding factor. However, more patients, including patients with high-risk MM, are achieving quality responses with targeted therapy regimens compared with conventional chemotherapy, and there is compelling evidence that achieving a quality response can at least partially overcome the impact of negative prognostic factors, including cytogenetic abnormalities. This is particularly evident in the more recent non-transplant studies where HD-ASCT is not an option, and aggressive treatment with targeted therapies has been shown to improve the quality of response and outcomes in high-risk patients. These studies have generally demonstrated important associations between the quality of response and outcomes (Table 2),^{9,31,43,58–63} and pooled analyses have allowed for more

robust subgroup analyses to better examine the potential impact of selection bias.^{30,31}

Gay *et al.*³¹ conducted a pooled analysis of three phase 3 studies that treated 1175 patients with MP with or without thalidomide (GISMM-2001¹⁷ and HOVON 49⁶⁴ studies) and/or bortezomib (GIMEMA-MM-03-05⁶⁵). The highest CR rate was observed in patients receiving VMPT plus VT maintenance (49%) with the lowest rate in patients receiving MP (5%), with a robust association between depth of response and outcomes. The 3-year OS rate was 91% for CR compared with 70% for VGPR ($P < 0.001$), and 67% for PR ($P < 0.001$). These relationships were maintained in subgroups older and younger than 75 years of age, and after adjustment for other prognostic factors with multivariate analysis. The time to achieve a CR did not have a significant impact on the outcomes.

More recently, Gay *et al.*³⁰ conducted a separate pooled analysis of 771 patients enrolled in the GIMEMA-MM-03-05⁶⁵ and GEM05MAS65²¹ studies, which assessed the combinations of bortezomib with an IMiD for induction and the use of bortezomib regimens for maintenance therapy. In response-evaluable patients ($n = 751$), 36% achieved a CR, 19% a VGPR and 32% a PR. Baseline age, ISS stage and cytogenetics—t(4;14), t(14;16) and del17p—were similar across these response subgroups. In a landmark analysis using a 12-month time point, the OS rate at 3 years was 75% overall and 94% in the CR subgroup versus 86% in the VGPR subgroup (hazard ratio (HR) 0.30, 95% confidence interval (CI) 0.16–0.52, $P < 0.001$). The 3-year OS rate was superior for standard-risk versus high-risk cytogenetics overall (76 versus 65%; HR 0.65, 95% CI 0.47–0.91, $P = 0.01$), but in patients with a CR, the rates did not differ (94% versus 90%, respectively; HR 0.66, 95% CI

Table 2. Prognostic impact of response level in patients with newly diagnosed multiple myeloma: non-transplant studies

Reference Response criteria Study type	Treatment	Response	n	PFS/TTP/EFS (median, mo ^a /rate, %)			OS (median, mo ^a /rate, %)		
Kyle <i>et al.</i> ⁴³ ECOG Ph 3 post hoc	VBMCP ± IFN or HD-Cyc	CR PR	85 335	—	—	—	mOS 61.2 ^b , 39.6 ^b	—	P -value < 0.0001
Offidani <i>et al.</i> ⁵⁹ EBMT Ph 2	ThaDD	≥ VGPR < VGPR	28 22	EFS	3 yr 78 ^c 37 ^c	P -value 0.021	OS	3 yr 84 61	P -value 0.053
Palumbo <i>et al.</i> ⁶¹ EBMT Ph 1/2	MPR	CR/VGPR PR/MR	20 33	EFS	1 yr 100 88	0.034	—	—	—
Harousseau <i>et al.</i> ⁶⁰ EBMT Ph 3 post hoc	VMP arm only	CR PR	102 136	mTTP NR	—	0.004 ^d	mOS 46.2 NR	—	0.54 ^d
Gay <i>et al.</i> ³¹ IMWG Pooled analysis of three Ph 3 studies	MP, MPT, VMP or VMPT → VT	CR VGPR PR	195 212 397	PFS	3 yr 67 27 27	P -value < 0.001 CR versus VGPR and versus PR	—	3 yr 91 70 67	P -value < 0.001 CR versus VGPR and versus PR
Oivanen <i>et al.</i> ⁹ CLMTF Pooled analysis of four prospective studies	MP or combination chemotherapy	Age ≤ 70 yr CR 75% Response PR MR SD PD Age > 70 yr CR 75% Response PR MR SD PD	21 95 101 42 16 49 8 26 37 10 6 20	—	—	—	mOS 63 58 59 49 57 10 44 44 40 32 22 4	—	< 0.0001 for any category versus PD ≤ 0.003 for any category versus PD

Abbreviations: CLMTF, Chronic Leukemia-Myeloma Task Force; EBMT, European Group for Blood and Marrow Transplantation; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HD, high dose; mOS, median overall survival; MP, melphalan, prednisone; mPFS, median progression-free survival; MPT, melphalan, prednisone, thalidomide; mTTP, median time to progression; MPR, melphalan, prednisone, and lenalidomide; NR, not reached; ThaDD, thalidomide, dexamethasone and pegylated liposomal doxorubicin; VBMCP, vincristine, carmustine (BCNU), melphalan, cyclophosphamide and prednisone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; VT, bortezomib, thalidomide; yr, years. ^aConversion to months for studies reporting other time increments. ^bFrom time of response, converted from years to months. ^cLandmark analysis after 4 months of treatment. ^dMultivariate analysis.

0.29–1.50, $P=0.32$). A similar trend was seen in a subgroup analysis by ISS stage—significant differences between the ISS stages when considering all evaluable patients, but no difference for patients with a CR. The prognostic significance of CR versus VGPR was maintained following multivariate analysis (HR 0.24, 95% CI 0.10–0.55, $P<0.001$). Thus, quality of response was a more robust predictor of survival than cytogenetics or ISS stage. Nonetheless, the potential confounding impact of salvage therapies cannot be ruled out, although in maintenance therapy trials variations in treatment after induction can be better controlled because of long-term treatment protocols. Improvement in OS in the context of maintenance trials represents the highest level of evidence achievable in clinical practice.

Relapsed and/or refractory

In the relapsed or refractory setting, studies have also shown associations between depth of response and outcomes, although data are limited (Table 3).^{32,58,66–71} In the phase 3 APEX study, bortezomib was superior to high-dose dexamethasone for patients with relapsed MM with respect to response results, time to progression and OS.¹⁴ An exploratory analysis of the bortezomib arm ($n=315$) showed no statistical difference in median TTP among patients who achieved a CR (9.7 months) compared with a VGPR (10.8 months) or a PR (8.5 months), whereas CR was associated with significant improvements in the median treatment-free interval (24.1 months) compared with VGPR (6.9 months, $P=0.007$) and PR (6.4 months, $P=0.002$).⁶⁶ This was likely due in part to the design of the study—once patients achieved a CR, they continued treatment for only two additional cycles. Finally, patients who achieved an MR had a significantly longer TTP compared with non-responders (4.9 versus 2.8 months, $P=0.016$) and there was a trend of improved OS (24.9 versus 18.7 months).

Other studies have also demonstrated the benefit of achieving an MR in the relapsed/refractory setting. A pooled analysis of

two phase 2 studies using thalidomide-containing regimens in patients with relapsed MM showed an association between the level of response and OS with a median OS of >70 months for achievement of \geq VGPR, 35 months for PR and 11.7 months for MR or non-response ($P<0.001$).⁶⁹ MR was favored over non-response for PFS (6.1 versus 3.8 months) but not for OS (11 versus 14 months). In a phase 2 study of carfilzomib in patients with relapsed and refractory MM ($n=266$), median PFS was 10.6 months for patients achieving \geq VGPR ($n=14$), 8.3 months for PR ($n=47$) and 9.6 months for MR ($n=34$), whereas the median for the response-evaluable population overall ($n=257$) was 3.7 months.⁷²

IMPROVING THE QUALITY OF RESPONSE AND OUTCOMES

Despite positive trends in treatment outcomes over the past decade, it has become apparent that treatment strategies need to be further developed to improve the depth and durability of response for the individual patient with MM, particularly those with high-risk disease, where the risk of increased toxicity with prolonged or more aggressive treatment is outweighed by the potential survival benefit.⁷³ Patients with high-risk cytogenetic abnormalities generally have a shorter duration of response, PFS and OS than standard-risk patients, but the benefit of a CR can be more pronounced.^{11,74} Given that 25–30% of the NDMM patients present with high-risk disease,⁷⁵ efforts have been made to improve the quality of response and outcomes in these patients, including maintenance therapy and combinations of targeted therapies.

Maintenance therapy

A number of studies have investigated the efficacy and safety of maintenance treatment with targeted therapies.^{76–82} Studies have consistently demonstrated that thalidomide maintenance after HD-ASCT improves the quality of response and PFS, and some

Table 3. Prognostic impact of response level in patients with relapsed or refractory multiple myeloma

Reference Response criteria Study type Patients	Treatment	Response	n	PFS/TTP/EFS (median, mo ^a /rate, %)	OS (median, mo ^a /rate, %)
Niesvizky <i>et al.</i> ⁶⁶ mEBMT Ph 3 <i>post hoc</i> Relapsed	BTZ arm	CR VGPR PR MR non-response	27 31 77 21 159	mTTP 9.7 10.8 8.5 4.9 2.8 P-value — 0.016 MR versus non-response	mOS NR NR NR 24.9 18.7 P-value —
Palumbo <i>et al.</i> ⁶⁷ IMWG Observational Relapsed or refractory	VD + Dox or PLD	\geq VGPR PR	16 27	EFS — 1 yr 83 16 P-value 0.02	OS — 1 yr 90 63 P-value 0.06
Pineda-Roman <i>et al.</i> ⁶⁸ Ph 1/2 Relapsed or refractory	VT ± D	\geq MR <MR	62 20	— — — — P-value —	OS — 1 yr 73 20 P-value <0.0001
Quach <i>et al.</i> ⁶⁹ EMBT Pooled analysis of two Ph 2 studies Relapsed or refractory	T + IFN or T + celecoxib	\geq VGPR PR MR or non-response MR non-response	9 47 48 18 30	mPFS 69 14 4 6.1 3.8 P-value — <0.001 PR versus MR or non-response	mOS >70 35 11.7 11 14 P-value — <0.001 PR versus MR or nonR
Harousseau <i>et al.</i> ³² mEBMT Retro of two Ph 3 trial Relapsed or refractory	RD arm	CR/VGPR PR	114 100	mTTP 27.7 12.0 P-value <0.001	mOS NR 44.2 2 yr 59.6 42.0 P-value 0.021

Abbreviations: BTZ, bortezomib; EFS, event-free survival; IFN, interferon; IMWG, International Myeloma Working Group; mEBMT, modified European Group for Blood and Marrow Transplantation; mo, months; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; NR, not reached; nonR, non-response; RD, lenalidomide and dexamethasone; T, thalidomide; VD, bortezomib, dexamethasone; VGPR, very good partial response; yr, years. ^aConversion to months for studies reporting other time increments.

studies have also shown an OS benefit.⁸³ However, there is concern about cumulative neurotoxicity with thalidomide.

Lenalidomide maintenance has been assessed in three randomized controlled trials.^{76–78} In one phase 3 trial, 460 patients who had achieved at least stable disease with HD-ASCT were randomized to maintenance with lenalidomide or placebo.⁷⁷ Lenalidomide maintenance was associated with significantly improved TTP compared with placebo (46 versus 27 months; $P < 0.001$) and OS with a 3-year rate of 88% versus 80% ($P = 0.03$). This benefit was notable in patients who had not achieved CR with HD-ASCT. In patients who achieved CR with HD-ASCT, the median TTP was not reached in the lenalidomide maintenance arm versus 36 months in the placebo arm (natural log HR 0.53, 95% CI -0.001 – 1.1), with corresponding values of 43 versus 23 months in the non-CR subgroup (natural log HR 0.86, 95% CI 0.53– 1.2 ; P for interaction = 0.38). Lenalidomide maintenance was also associated with improved OS in both subgroups, and again the benefit was more pronounced in the non-CR subgroup (natural log HR 0.53, 95% CI 0.05– 1.0 ; P for interaction = 0.64 .) than in the CR group (natural log HR 0.25, 95% CI -0.67 – 1.2). Lenalidomide maintenance was associated with increased toxicity, including grade 3/4 hematologic events (48% versus 17%, respectively, $P < 0.001$) and secondary primary malignancies (8% versus 3%, respectively; $P = 0.008$). In the other two studies, lenalidomide maintenance improved PFS, particularly among transplant-eligible patients who achieved \geq VGPR with HD-ASCT⁷⁸ and transplant-ineligible patients < 75 years of age.⁷⁶ There was no improvement in OS in either of these studies, but the investigators from both studies noted the need for longer follow-up.

Bortezomib may also be beneficial as a maintenance therapy.^{80–82,84} Sonneveld *et al.*⁸¹ recently reported results of a phase 3 study in 827 patients with NDMM who were randomized to induction with VAD or bortezomib, doxorubicin and dexamethasone, followed by HD-ASCT and maintenance with thalidomide for VAD and bortezomib for bortezomib, doxorubicin and dexamethasone. The CR rate overall was 24% for the VAD arm versus 36% for the bortezomib, doxorubicin and dexamethasone arm ($P < 0.001$), the rate of improved response during maintenance treatment was 24% and 23% ($P = 0.64$), respectively. Median PFS was 28 versus 35 months, respectively ($P = 0.002$), and median OS had not been reached in either arm. Subgroup analysis of patients with the 17p13 deletion showed a \geq nCR rate of 20% in the VAD arm versus 52% in the bortezomib, doxorubicin and dexamethasone arm ($P = 0.008$), which corresponded to median OS of 24 versus > 54 months (HR 0.36, 95% CI 0.18– 0.74 ; $P = 0.003$). In the subgroup without the 17p13 deletion, there was no difference in OS (HR 0.96, 95% CI 0.69– 1.34 ; $P = 0.81$).

As data for maintenance therapy accumulate, it will be important to assess the impact quality of response has on outcomes in different risk groups. Although there is compelling evidence that driving response deeper with maintenance therapy in standard-risk patients improves PFS and possibly OS,^{26,55} PFS is not a suitable surrogate for OS in this patient population.^{15,78,85,86} Without prolonged follow-up and OS data, it is unclear if those achieving CR after HD-ASCT should receive maintenance treatment or wait until relapse. In high-risk patients where CR has been shown to be an important predictor of outcome, PFS is a suitable primary endpoint as it usually correlates with OS.^{11,30,87} For high-risk patients, it is not so much a question of maintenance therapy but rather if a multidrug combination is appropriate.^{80,83,84,87}

Multidrug treatment strategies—combining PIs and immunomodulatory drugs

Pairing PIs with IMiDs or cytotoxic agents, usually in triplet combinations with a corticosteroid, is changing the treatment landscape in MM as factors associated with poor outcomes appear

to have far less impact.⁸⁸ The rationale for using these combinations is supported by the preclinical data demonstrating that IMiDs potentiate the activity of PIs and dexamethasone^{89–92} and of synergistic activity between PIs and cytotoxic agents.^{93–95} Many of the toxicities associated with these drug classes are non-overlapping. So far, triplet combinations with a PI, IMiD and corticosteroid have demonstrated exceptional responses in both the frontline and salvage settings, and in patients with high-risk disease (Table 4).^{19–24,96–99} Generally, these combinations have been well tolerated, as high anti-MM activity has allowed the development of regimens with reduced doses or different dosing schedules of the individual agents.^{20,22,24,98} Nonetheless, there are increases in some toxicities, and there may be limits to the combinations currently available. In the phase 2 EVOLUTION study, for example, a quadruplet combination of bortezomib, dexamethasone, cyclophosphamide and lenalidomide was highly active in NDMM but did not provide a clinical benefit over bortezomib-based triplet combinations and was associated with greater toxicity.¹⁰⁰ Other than the pooled analysis of the GIMEMA-MM-03-05 and GEM05MAS65 studies discussed earlier,³⁰ the impact of quality of response on outcomes has not been well studied with these combination regimens.^{19,30}

REDEFINING CR—IMMUNOPHENOTYPIC AND MOLECULAR CR

As the rates of CR and stringent CR continue to advance, it is of interest to further stratify the CR category. Assessment of minimal residual disease (MRD) in bone marrow plasma cells with sensitive assays that define immunophenotypic and molecular responses is becoming a useful measure of response with potential prognostic implications.^{21,56,101–105} Immunophenotypic response is assessed by multiparametric flow cytometry, which uses immunofluorescence with monoclonal antibodies to plasma cell proteins (for example, CD38, CD19 and CD117) to identify, quantify and characterize bone marrow plasma cell composition.^{101–103} Molecular response is assessed with allele-specific oligonucleotide PCR. Tumor-specific primers are constructed for individual patients from the rearranged variable region of immunoglobulin heavy-chain genes through reverse transcription of RNA (extracted from bone marrow plasma cells) and generation of the immunoglobulin heavy-chain genes complementary DNA.^{56,106}

In a prospective analysis of 295 patients with NDMM uniformly treated with the GEM2000 protocol, the immunophenotypic response was assessed by the multiparametric flow cytometry method (sensitivity 10^{-4}) at 100 days post transplantation.¹⁰³ At day 100, 147 patients had achieved a CR, with 58% being MRD positive and 42% MRD negative. In the MRD-positive group, the proportion of abnormal plasma cells corresponded to depth of response, with a mean of 0.10% for CR, 0.21% for nCR and 0.76% for PR ($P = 0.001$). PFS was significantly longer for MRD-negative versus MRD-positive patients (median, 71 versus 37 months, $P < 0.001$), as was OS (5-year rate of 82 versus 60%, $P = 0.002$), with the benefit independent of immunofixation status. For the immunofixation-negative subgroup (that is, CR), the 5-year PFS rate was 62% in MRD-negative versus 30% in MRD-positive patients ($P < 0.001$) and the 5-year OS rate was 87% versus 59%, respectively ($P = 0.009$).

Ladetto *et al.*⁵⁶ assessed MRD by the nested-PCR method (sensitivity 10^{-6}) in 39 patients with NDMM who achieved a \geq VGPR with HD-ASCT received consolidation therapy with bortezomib, thalidomide, dexamethasone. At study entry, 33 patients (85%) had a VGPR following HD-ASCT, 6 had a CR (15%) with 1 (3%) a molecular CR. All patients received one course of bortezomib, thalidomide, dexamethasone and 31 completed four courses. After consolidation, the CR rate improved to 49% and molecular CR improved to 18%. After a median follow-up of 42

Table 4. Clinical studies in patients with multiple myeloma receiving combination regimens that include a proteasome inhibitor and an IMiD

Reference Response criteria Study type	Treatment arm	n	Maximal response (%)	PFS/TTP (median, mo ^a /rate, %)	OS (median, mo ^a /rate, %)	
Frontline transplant eligible						
Cavo <i>et al.</i> ¹⁹ mEBMT Ph 3	VTD induction/consolidation	241	CR induction 19	Overall 58	3-yr PFS 68	3 yr 86
	TD induction/consolidation	239	5	41	56	84
				<i>P</i> < 0.0001	<i>P</i> = 0.0001	<i>P</i> = 0.0057
Moreau <i>et al.</i> ²⁰ IMWG Ph 3	vtD induction		CR induction 13	Transplant 29	mPFS 26	—
	VD induction		12	31	30	
			<i>P</i> = 0.74	<i>P</i> = 0.77	<i>P</i> = 0.22	
Transplant ineligible						
Palumbo <i>et al.</i> ⁶⁵ IMWG Ph 3	VMPT induction → VT maint	254	CR induction 38	mPFS NR	3-yr PFS 56	3 yr 89
	VMP induction	257	24	27.3	41	87
			<i>P</i> < 0.001		<i>P</i> = 0.008	<i>P</i> = 0.77
Mateos <i>et al.</i> ²¹ mEBMT Ph 3	VTP induction → VT or VP maint	130	CR induction 28	mPFS 25	3 yr 65	
	VMP induction → VT or VP maint	130	20	34	74	
			<i>P</i> = 0.2	<i>P</i> = 0.1	<i>P</i> = 0.3	
Transplant eligible/ineligible						
Richardson <i>et al.</i> ²² mIMWG Ph 1/2	VRD induction → VRD maint or HD-ASCT	66	CR overall 29	18-mo PFS 75	18 mo 97	
Jakubowiak <i>et al.</i> ²⁴ mIMWG Ph 1/2	CRd induction → CRd maint or HD-ASCT	53	sCR overall 42	2-yr PFS 92	—	
Kumar <i>et al.</i> ²⁵ mIMWG Ph 1/2	IRd → ixazomib maint	65		CR overall 18	—	—
Relapsed						
Garderet <i>et al.</i> ²³ mEBMT Ph 3	VTD	135	CR overall 25	mTTP 19.5	24 mo 71	
	TD	134	14	13.8	65	
			<i>P</i> = 0.024	<i>P</i> = 0.001	<i>P</i> = 0.093	

Abbreviations: CRd, carfilzomib, lenalidomide, low-dose dexamethasone; HD-ASCT, high-dose therapy with autologous stem cell transplant; IRd, ixazomib (MLN9708), lenalidomide, low-dose dexamethasone; maint, maintenance therapy; mEBMT, modified European Group for Blood and Marrow Transplantation; mIMWG, modified International Myeloma Working Group; mo, months; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; TD, thalidomide, dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; vtD, low-dose bortezomib, thalidomide with dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; VTP, bortezomib, thalidomide, prednisone; yr, years. ^aConversion to months for studies reporting other time increments.

months, all patients who achieved a molecular response were relapse-free, whereas 11 patients who were MRD-positive had relapsed.

These new assays will be critical in determining the benefit of aggressive and prolonged therapies, and are potential surrogate markers for OS. In 2011, the International Myeloma Working Group updated the response criteria to include immunophenotypic CR, defined as a stringent CR with evidence of MRD-negative disease by multiparametric flow cytometry (absence of phenotypically aberrant clonal plasma cells in ≥ 1 million analyzed cells), and molecular CR, a CR with evidence of MRD-negative disease by the PCR method (sensitivity 10^{-5}).¹⁰⁷ Although a number of studies are now using MRD as a study endpoint,^{21,24,100,108} these assays are complex, not applicable to all patients and allele-specific oligonucleotide PCR can be expensive and time consuming, so their wider adoption may take time.

FUTURE CONSIDERATIONS

The development of targeted therapies for MM has not only resulted in clinically significant improvements in outcomes but has also advanced our understanding of this complex disease. Collectively, the results from studies of targeted therapies support maximizing response at all treatment stages and in most patient subgroups. However, these are not definitive data and there remain important gaps in our knowledge. We need to more accurately predict the individual response level that is durable and will extend disease control and survival without significant risk of treatment-related morbidity. Some patients can achieve long-term

survival with a lesser response, but this may or may not require continuous treatment, and the potential benefit of treating a patient to a deeper response with more aggressive treatment of shorter duration should also be weighed. Treatment decisions—initiating a new treatment or intensifying the current treatment—need to be better informed across the levels of response.¹⁰ This will require a greater understanding of the molecular evolution of MM over the course of the disease and treatment, to identify and differentiate high- to low-risk subclones and their sensitivity to the selective pressures of specific treatments at initial diagnosis and disease progression.^{33–35} This could lead to strategies that primarily target the highly proliferative and genetically dynamic subclones with aggressive multi-agent treatment, and secondarily target indolent and genetically stable subclones with more selective regimens but this will require further study in the clinical setting. Finally, the cost of targeted therapies—particularly, prolonged treatment (for example, maintenance or salvage therapy)—is an important barrier that should be acknowledged, as some healthcare systems may not provide support for their use in certain settings without definitive data.

In the transplant setting, the development of triplet combinations pairing PIs and IMiDs has improved the depth of response with induction therapy. Triplet combinations allow for more rapid and high-level responses, and may overwhelm the potential resistance through synergistic and complementary antimyeloma activity.⁸⁸ The quality of response with some triplet combinations has reached a level where it might be better to defer HD-ASCT until relapse or use it strategically to improve response.¹⁰⁹

Ongoing studies should help to address these issues (ClinicalTrials.gov NCT01191060 and NCT01208766).

Although tolerability with multidrug regimens is always a concern, various treatment strategies (for example, attenuated dosing⁵) are available to address these in specific patients and will help to broaden the spectrum of patients considered for multidrug regimens. Furthermore, novel PIs (for example, carfilzomib and ixazomib [MLN9708]) and IMiDs (for example, pomalidomide) have demonstrated good clinical activity and are well tolerated,^{24,25,72,98,99,110,111} and other classes of targeted therapy (for example, histone deacetylase inhibitors and monoclonal antibodies) have shown encouraging activity.^{112,113} With more options, treatment regimens can be better tailored to the individual patient.

The development of laboratory and animal models of myeloma and the bone marrow microenvironment in the 1990s proved instrumental in rapidly bringing the targeted therapies from the bench to the bedside and in the development of combination regimens.¹⁸ Moving forward, preclinical models will help us to better understand the mechanisms underlying the quality of responses, to develop biomarkers that predict treatment response and outcomes, and to maximize the potential of targeted therapies. It is equally important to continue to develop response assays that can further differentiate the impact of high-level response and are accessible to a range of institutions.

CONCLUSIONS

In the era of targeted therapies, quality of response is associated with disease control and survival in patients with MM, including patients with high-risk disease, but until clinical trials are specifically designed to assess this relationship, it will remain only an association. Achievement of maximal response should be considered upfront and at all stages of treatment, bearing in mind tolerability, quality of life and treatment barriers including cost and the lack of definitive data. In select patients, achievement of a lesser response may be adequate to prolong survival and attempts to treat these patients to a better response may place them at unnecessary risk without a significant benefit. Multidrug regimens combining PIs with IMiDs have improved depth of response, have acceptable tolerability and are becoming a standard treatment approach. The development of novel targeted therapies should further advance these goals as clinical data in conjunction with laboratory findings should help to facilitate the use of antimyeloma agents to their fullest potential. Treatment should be tailored to the disease characteristics and needs and goals of the individual patient.

CONFLICT OF INTEREST

Dr Lonial has received compensation as a consultant for Millennium, Celgene, Novartis, Bristol-Myers Squibb, Onyx Pharmaceuticals and Merck. Dr Anderson has received compensation as a member of the scientific advisory boards of Celgene, Onyx, Gilead, and Sanofi-Aventis. He is also a scientific founder of Acetylon and Oncopep.

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